REMARKS

The undersigned is positive that he appended to the previous amendment a copy of Fig. 4 to which were added Comparison Examples 4-6 as well as "increase factors" with Comparison Example 4 as a baseline. Another copy thereof is appended hereto.

Claim 1 has been amended to be consistent with claim 13.

The following is submitted in response to the 35 U.S.C. 112, second paragraph rejection.

C_7 - sulfonic acids have been deleted from claim 4. Regarding claims 6 and 23, please note that hexanesulfonic acid is not a tosylate. A tosylate comprises $CH_3C_6H_4SO_3O$-, a residue consisting of 7 carbon atoms, whereas a hexanesulfonic acid residue consists of 6 carbon atoms only. Furthermore, "hexanesulfonic acid" undoubtedly demotes an aliphatic molecule whereas tosylates comprise a ring structure.

The 35 U.S.C. 103(a) rejection based on US '529 or '297 is respectfully traversed.

It is known that opioids poorly penetrate human skin, regardless of whether they are present as free base or as salt. Further, there is no information available which would suggest to a skilled artisan selection of organic acids for preparing an acid addition salt of a morphine alkaloid that possesses the desired improved skin permeability as defined in claims 1 and 13. Therefore, a skilled artisan would not have reasonably expected that the acid addition salts of the present invention would permeate the skin with a flux of at least 2.34 $\mu g/cm^2 \cdot h$. Further support is provided by the attached table which illustrates that different acids yield acid addition salts of morphine alkaloids possessing substantially the same flux (compare the nicotinate and oxo-prolinate), whereas some salts possess substantially the same flux as the free base.

It is submitted that the feature of a flux of at least 2.34 $\mu g/cm^2 \cdot h$ is suitable to distinguish chemical substances from one another. Therefore, this feature is considered to be suitable not only to distinguish the acid addition salts of morphine alkaloids according to the present invention from acid addition salts of morphine alkaloids known in prior art, but is suitable to express inventiveness of the present invention as well.

The Examiner did not comment on the subject matter of the claims directed

to the acid addition salts of the morphine alkaloid themselves (claims 13, and 26 to 30). Cited References US 4,626,539 and US 4,879,297 are directed to pharamaceutical compositions and permeation enhancers rather than to the acid addition salts of morphine alkaloids themselves. These references did not make the acid addition salts of the present obvious to the skilled artisan at the time the present invention was made. This is further reason the subject matter of claims 13 and 26 to 30 should be allowable.

Moreover, given that the acid addition salts of morphine alkaloids are novel and non-obvious, then their use for pharmaceutical compositions comprising these acid addition salts of morphine alkaloids has to be considered novel and non-obvious as well.

Respectfully submitted,
JORDAN AND HAMBURG LLP

By _____
C. Bruce Hamburg
Reg. No. 22,389
Attorney for Applicants

Jordan and Hamburg LLP
122 East 42nd Street
New York, New York 10168
(212) 986-2340

Comparison skin permeation of various morphine salts

Type of skin: nude guinea pig (back); # 20/05-0455/00-95
Acceptor: 0.9% NaCl solution + 0.1% NaN3
Release temperature: 37 °C
Release vehicle: olive oil
Load donor: 2 Ma%; relative to Mph salt I
Load Mph salt/cm² skin: 787.4 µg
Unit of values: µg/cm² (mean values of n=3)
* Flux: sum 48 h (accumulated) – sum 24 h (accumulated) / 24
Unit of values flux: µg/cm²xh

	Mph salt	differential permeation values 7.5 h	24 h	30 h	48 h	total	flux*	increase factor
Example 1	monomethyl sebacate	3,31	12,3	7,47	24,6	47,7	1,34	3X
Example 2	p-hydroxybenzoate	24,2	172	82	196	474	11,6	26 X
Example 3	oxo-prolinate	9,82	71,2	47,4	172	301	9,16	20 X
Example 4	hexane sulfonate	2,7	18,7	14,4	63,6	99,4	3,25	7 X
Example 5	nicotinate	22,2	99,9	55,4	167	345	9,29	20 X
Example 6	p-aminobenzoate	8,56	23,6	10,5	45,6	88,3	2,34	5 X
Example 7	trimethylbenzoate	3,7	36,3	24	102	166	5,25	12 X
Example 8	liponate	1,23	12,0	8,52	19,9	41,6	1,18	2,5X
Example 9	acetyl glycinate	38,1	180,0	62,4	110	390	7,17	16 X
Example 10	hippurate	22,9	83,4	41,3	109	256	6,25	14 X
Comparison Expl. 1	[base]	3,54	3,2	2,48	8,3	17,5	0,45	
Comparison Expl. 2	propionate	1,55	4,74	2,66	8,54	17,5	0,47	1X
Comparison Expl. 3	formiate	0,342	6,46	2,54	8,6	17,9	0,46	1X

Skin permeation values of known morphine salts
Type of skin: bovine udder, dermatomized 1200 µm

Comparison Expl. 4	[base]	0,96	5,32	2,75	8,10	17,1	0,45	
Comparison Expl. 5	salicylate	2,18	14,6	6,86	16,0	39,6	0,95	2 X
Comparison Expl. 6	4-tosylate	4,82	21,9	10,2	27,3	64,2	1,56	3,5 X